Remarks

Claims 1-96 are pending in this application. By this Amendment, applicants have amended claims 1, 16-21, 26-27, 40-45, 47, 55, 62-67, 72, 73, 86-91, and 93-96. Applicants have also canceled claims 46, 54, 78 and 92 without prejudice to applicants' rights to pursue the subject matter of these claims in this or a related application. In addition, applicants have added new claims 97-105. Therefore, claims 1-45, 47-53, 55-77, 79-91 and 93-105 are pending in this application. Claims 4, 5, 25, 28, 29, 50, 51, 74 and 75 have been withdrawn from consideration as being drawn to a nonelected species.

Support for the amendment to claims 1 and 93 may be found, *inter alia*, on page 2, lines 18-21, page 6, lines 5-30, page 8, lines 33-34, page 9, line 1 and page 10, lines 18-19 and 28-30 of the subject specification.

Support for the amendment to claims 16 and 40 may be found, *inter alia*, on page 10, lines 18-19 and 26-30 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 17 and 41 may be found, *inter alia*, on page 10, lines 29-30 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 18 and 42 may be found, *inter alia*, on page 10, lines 30-31 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 21 and 45 may be found, *inter alia*, on page 10, lines 30-31 of the subject specification, in

accordance with to MPEP §2163.05(III).

Support for the amendment to claims 47 and 94 may be found, *inter alia*, on page 2, lines 18-21, page 6, line 32 to page 7, line 23, page 8, liners 33-34, page 9, line 1 and page 11, lines 2-3 and 13-14 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claim 55 may be found, *inter alia*, on page 8, lines 33-34 of the subject specification.

Support for the amendment to claims 62 and 86 may be found, *inter alia*, on page 11, lines 2-3 and 11-12 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 63 and 87 may be found, *inter alia*, on page 11, lines 13-14 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 64 and 88 may be found, *inter alia*, on page 11, lines 14-15 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claims 67 and 91 may be found, *inter alia*, on page 11, lines 14-15 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claim 95 may be found, *inter alia*, on page 10, lines 18-19 and 28-30 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for the amendment to claim 96 may be found, *inter alia*,

on page 11, lines 2-3 and 13-14 of the subject specification, in accordance with to MPEP §2163.05(III).

Support for new claims 97 and 99 may be found, *inter alia*, on page 9, lines 1-6 of the subject specification.

Support for new claims 98 and 100 may be found, *inter alia*, on page 9, line 3-6 of the subject specification.

Support for new claims 101 and 102 may be found, *inter alia*, on page 2, lines 12-15 of the subject specification.

Support for new claim 103 may be found, *inter alia*, on page 2, lines 4-7 of the subject specification.

Support for new claims 104 and 105 may be found, *inter alia*, on page 11, lines 26-27 of the subject specification.

Rejections under 35 USC § 112, First Paragraph

The Examiner rejected claims 47-92, 94, and 96 under 35 U.S.C. § 112, first paragraph, alleging that, while the specification is enabling for headache, migraine, and neuropathic pain, it does not reasonably provide enablement for other types of pain. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner alleged that, in the instant case, the claims are directed to a method of preventing pain by employing the herein claimed valproic acid derivative. The Examiner alleged that the

specification discloses the method of treating allodynia by employing the herein claimed compound. However, the Examiner alleged that the specification fails to adequately teach how to use the method to prevent such pain. The Examiner alleged that the only example discussing preventing of pain is experimental example 2, page 17-19, in the instant specification. However, the Examiner alleged that this example only demonstrates the efficacy of treating allodynia (a painful condition) when the animals have already suffered from pain. The Examiner alleged that no example is set forth in the instant specification on prevention of pain by employing the herein claimed compounds before pain occurred. The Examiner alleged that the term, "pain," encompasses conditions with vastly different etiologies, such as trauma, surgery, neuropathic, infection, and even psychological origin. The Examiner alleged that applicants have not provided convincing evidence that their claimed invention is useful as preventive for all pain and allegedly have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention without undue experimentation. In the alleged absence of such guidance and evidence, the Examiner asserted that the specification allegedly fails to provide an enabling disclosure.

In reply, applicants have canceled claims 54, 78 and 92 without prejudice to applicants' rights to pursue the subject matter of these claims in this or a related application. Applicants have also amended independent claims 47, 93 and 94 by adding the phrase, "wherein the pain is neuropathic pain, a migraine or a headache disorder." The Examiner acknowledged that the specification enables prophylaxis of neuropathic pain, migraine and headache disorder. Thus, amended claims 47-49, 52-73, 76-92, 94, and 96, which are directed to prophylaxis of neuropathic pain, migraine and headache disorder, are enabled. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of

claims 47-49, 52-73, 76-92, 94, and 96 under 35 USC § 112, first paragraph.

Rejections under 35 USC § 112, Second Paragraph

The Examiner rejected claims 26-29, 47-92, 94, and 96 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner noted that claims 26-29 and 72-75 recite the limitation "R_4" in line 2. The Examiner alleged that there is insufficient antecedent basis for this limitation.

The Examiner alleged that the expression, "a method of preventing pain," in claims 47, 94, and 96, renders the claims indefinite as failing to clearly set forth the metes and bounds of the patent protection desired. The Examiner alleged that examples of how and when to prevent pain are not set forth in the specification. The Examiner also alleged that the only example discussing preventing of pain is experimental example 2, page 17-19, in the instant specification. However, the Examiner alleged that this example only demonstrates the efficacy of treating allodynia (a painful condition) when the animals have already suffered from pain. The Examiner alleged that no example is set forth in the instant specification on prevention of pain by employing the herein claimed compounds before pain occurred. Absent such exemplication, the Examiner alleged that the skilled artisan could not establish the identity of those situations wherein prevention of pain would be effected. Furthermore, the Examiner alleged that it is unclear as to the degree of prevention (e.g., total prevention, some prevention, probable prevention, total prevention in most cases, etc.) herein because the specification does not disclose the extent

of prevention achieved. The Examiner indicated that a replacement of the term "prevention" with the term, "prophylaxis" would be favorably considered.

In response, applicants have amended claims 26-27 and 72-73 by deleting "R_4", thus remedying the lack of antecedent basis. Applicants note that claims 28-29 and 74-75 have been withdrawn from consideration as being drawn to a nonelected species. Additionally, applicants have adopted the Examiner's suggestion and amended claims 47, 94, and 96 to recite "a method of pain prophylaxis" instead of --a method of preventing pain--. Therefore, applicants respectfully request that the Examiner withdraw the rejection of claims 26-27, 47, 72-73, 94, and 96 under 35 USC § 112, second paragraph.

Rejections under 35 USC § 103

The Examiner rejected claims 1-3, 6-24, 26, 27, 30-49, 52-73, and 76-96 under 35 U.S.C. § 103(a) as allegedly unpatentable over Bialer et al. (US Patent No. 5,585,358 from the IDS received April 22, 2002) in view of Hansen (Southern Medical Journal, 1999, 92(7): 642-649), McQuay et al. (BMJ, 1995, 311: 1047-1052), Shank et al. (US Patent No. 5,760,007), Carrazana et al. (US Patent No. 6,319,903), Magnus (Epilepsia, 1999, 40(Suppl. 6): S66-S72), and Zakrzewska et al. (Pain 1997, 73(2): 233-230).

The Examiner alleged that Bialer et al. teach that the elected compound, N-(2-n-propylpentanoyl)glycinamide, is useful as an anticonvulsant for treating epilepsy and other neurological disorders, citing col. 7, lines 23-44; Example 1; col. 13, line 4 - col. 17, line 34 and the abstract. The Examiner alleged that Bialer et al. teach the effective dose in a composition for N-(2-n-propylpentanoyl)glycinamide as about 10 to about 500 mg citing col.

3, line 59-61. The Examiner additionally alleged that Bialer et al. also teach the ED_{50} dosage of N-(2-n-propylpentanoyl)glycinamide for antiepileptic activities as 73 mg/kg (about 5000 mg in an 70 kg adult), citing col. 13, line 39. The Examiner also alleged that Bialer et al. teach N-(2-n-propylpentanoyl)glycinamide can be administered through oral, intravenous, intraperitoneal, intramuscular, and topical routes, citing col. 7, lines 10-14. The Examiner also alleged that Bialer et al. teach that those skilled in the art would be able to determine the precise effective amount and routes of administration of the compound to be administered, citing col. 6, lines 49-59.

The Examiner acknowledged that Bialer et al. do not expressly teach N-(2-n-propylpentanoyl)glycinamide to be useful as treating or preventing acute, chronic, and neuropathic pain. The Examiner also acknowleged that Bialer et al. do not expressly teach the dosage of N-(2-n-propylpentanoyl)glycinamide as 6000 mg or 3000 mg. In addition, the Examiner acknowledged that Bialer et al. do not expressly teach the route of administration as intranasal, sublingual, inhalation, buccal, intravaginal, and pulmonary. The Examiner further acknowledged that Bialer et al. do not expressly teach the dosing frequency of N-(2-n-propylpentanoyl)glycinamide as periodic six times daily.

The Examiner alleged that Hansen teaches that various antiepileptic agents are useful in treating both acute and chronic pain, citing page 642, col. 2, second paragraph, page 646, col. 2, fourth paragraph to page 647, whole page.

The Examiner alleged that McQuay et al. teach that various anticonvulsants such as carbamazepine, phenytoin, and valproate sodium are effective in treating neuropathic pain such as trigeminal neuralgia and migraine prophylaxis in various degree,

citing the abstract, Tables 1-4; also citing the sections entitled "Trigeminal Neuralgia" and "Migraine Prophylaxis."

The Examiner alleged that Shank et al. teach that topiramate, an anticonvulsant, is useful in treating neuropathic pain, citing claim 2.

The Examiner alleged that Carrazana et al. teach that topiramate, an anticonvulsant, is useful in treating cluster headaches, citing claims 1-15.

The Examiner alleged that Magnus teaches that gabapentin, an anticonvulsant, is useful in treating neuropathic pain and useful in migraine prophylaxis, citing the summary; also citing page S66 to S68, first col. second paragraph and page S71, Table 5.

The Examiner alleged that Zakrzewska et al. teach that lamotrigine, an anticonvulsant, is useful in treating trigeminal neuralgia, a neuropathic pain, citing the abstract.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ N-(2-n-propylpentanoyl)glycinamide, in the herein claimed dosage and dosing regimen, in a method of treating and prophylaxis pain. The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer N-(2-n-propylpentanoyl)glycinamide in the herein claimed routes of administration.

The Examiner alleged that one of ordinary skill in the art would have been motivated to employ N-(2-n-

propylpentanoyl)glycinamide, in the herein claimed dosage and dosing regimen, in a method of treating pain and pain prophylaxis. The Examiner alleged that, based on the cited prior art, antiepileptic compounds with vastly different structures and mechanisms of action are useful for treating and preventing neuropathic pain, migraine headache and cluster headache. The Examiner alleged that the only common property of these antiepileptic compounds is that they are all useful as anticonvulsants. Therefore, the Examiner alleged that employing any known anticonvulsant, including N-(2-n-propylpentanoyl)glycinamide, would have been reasonably expected to be useful to treat or prevent neuropathic pain, migraine headache and cluster headache. Furthermore, the Examiner alleged that the optimization of result effect parameters (e.g., dosage range and dosing regimens) is obvious as allegedly within the skill of the artisan, based on the teachings of Bialer et al., citing col. 6, lines 49-59.

The Examiner alleged that one of ordinary skill in the art would have been motivated to administer N-(2-n-propylpentanoyl)glycinamide in the herein claimed routes of administration because one of ordinary skill in the art would be aware of all the conventional methods of administering a therapeutic compound. The Examiner asserted that selecting the herein claimed routes of administration over the alternatives would allegedly be obvious as allegedly within the purview of a skilled artisan.

In response, applicants point out that the only reference cited by the Examiner which specifically addresses applicants' compounds is Bialer et al. Bialer et al., however, fail to teach the use of applicants' compounds for the treatment or prophylaxis of pain as recited in applicants' amended claims

1-3, 6-24, 26-27, and 30-45 and new claims 101-105. Furthermore, there is no teaching or suggestion in Bialer et al. to use applicants' compounds for the treatment or prophylaxis of neuropathic pain, headache disorders or migraines as recited in applicants' amended claims 47-49, 52-53, 55-73, 76-77, 79-91, 93-96 and new claims 97-100 and 104-105, or for the treatment of cancer pain, postoperative pain, low back pain, complex regional pain syndrome, phantom pain, HIV pain, osteoarthritis pain, rheumatoid arthritis pain, diabetic peripheral neuropathy, postherpetic neuralgia, or trigeminal neuralgia as recited in new claims 101-103. Having not taught or suggested applicants' recited uses, Bialer et al. do not, as they cannot, teach or suggest applicants recited therapeutic or prophylactic dosage for the uses. Thus, Bialer et al. does not teach or suggest applicants' claims 1-3, 6-24, 26-27, 30-45, 47-49, 52-53, 55-73, 76-77, 79-91, and 93-105.

Furthermore, applicants assert that there is no reasonable expectation of success of at least doubling the dosage taught by Bialer et al. (about 10 to about 500 mg (column 3, lines 59-61)), to 1000 mg to 6000 mg as recited by applicants' claims, especially for indications not taught or suggested by Bialer et al., i.e., pain, generally, and specifically, neuropathic pain, headache disorders, migraines, cancer pain, postoperative pain, low back pain, complex regional pain syndrome, phantom pain, HIV pain, osteoarthritis pain, rheumatoid arthritis pain, diabetic peripheral neuropathy, postherpetic neuralgia, or trigeminal neuralgia.

The combination of Bialer et al. with the other cited references does not remedy the deficiencies of Bialer et al. The other cited references do not teach or suggest applicants' compounds, so they cannot and do not teach or suggest applicants' uses of

these compounds or applicants' recited dosage of these compounds.

Applicants also point out that none of the cited reference teach or suggest the use of any of the compounds recited in applicants' claims for the treatment or prophylaxis of tension-type headache, miscellaneous-type headache low back pain, complex regional pain syndrome, or osteoarthritis pain.

Applicants further note that the only reference which discloses the treatment of cluster headaches, not only uses different compounds than applicants' compounds, but teaches away from using applicants' valproic acid amide derivatives because in the two examples where valproate is mentioned, valproate was not effective in alleviating cluster headaches (see col. 6, lines 1-37). Thus, at a minimum, applicants contend that the combined references do not teach or suggest the use of applicants' compounds for the treatment or prophylaxis of cluster headache, tension-type headache, or miscellaneous-type headache low back pain, complex regional pain syndrome, or osteoarthritis pain as recited in claims 102-103.

For all of the above reasons, applicants assert that the amendments have addressed all of the issues raised by the Examiner and therefore, respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 103.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this

Amendment. However, if any fee is deemed necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

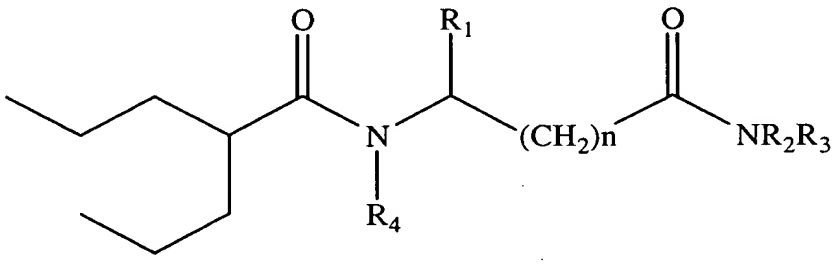
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Gary J. Gershik 3/31/03

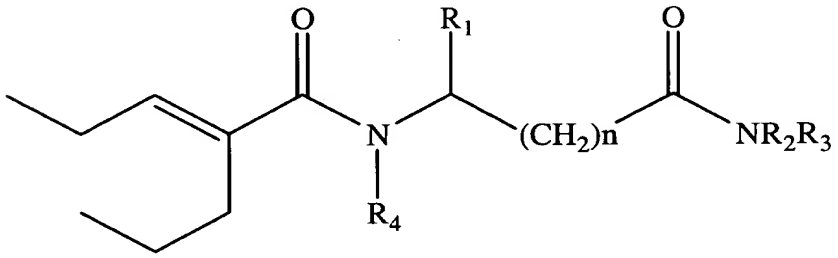
John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

Version with Markings to Show Changes Made

1. (Amended) A method of treating a subject suffering from pain comprising periodically administering to the subject a therapeutically effective dose of a compound having the following structure:



or



wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the therapeutically effective dose is 1,000 to 6,000 mg; so as to thereby treat the subject's pain.

16. (Amended) The method of claim 1, wherein the therapeutically effective dose is an amount from [about 10] 1,000 mg to [about 6,000] 4,000 mg.

17. (Amended) The method of claim 16, wherein the therapeutically effective dose is an amount from [about 500] 1,000 mg to [about 4,000] 3,000 mg.

18. (Amended) The method of claim [16] 17, wherein the therapeutically effective dose is an amount from [about 10] 2,000 mg to [about] 3,000 mg.

19. (Amended) The method of claim 18, wherein the therapeutically effective dose is [about] 3,000 mg.

20. (Amended) The method of claim 18, wherein the therapeutically effective dose is [an amount from about 10 mg to about] 1,000 mg.

21. (Amended) The method of claim 20, wherein the therapeutically effective dose is [an amount from about 50 mg to about 500] 2,000 mg.

26. (Amended) The method of claim 22, wherein one or more of R_1, R_2, or R_3 [or R_4] is a linear chain C_1-C_6 alkyl group.

27. (Amended) The method of claim 22, wherein one or more of R_1, R_2, or R_3 [or R_4] is a branched chain C_1-C_6 alkyl group.

40. (Amended) The method of claim 22, wherein the therapeutically effective dose is an amount from [about 10] 1,000 mg to [about 6,000] 4,000 mg.

41. (Amended) The method of claim 40, wherein the therapeutically effective dose is an amount from [about 500] 1,000 mg to [about 4,000] 3,000 mg.

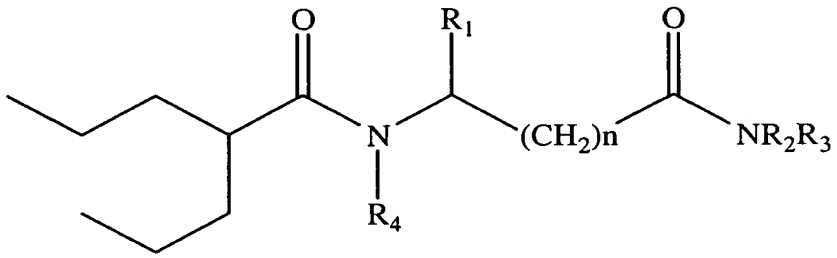
42. (Amended) The method of claim [40] 41, wherein the therapeutically effective dose is an amount from [about 10] 2,000 mg to [about] 3,000 mg.

43. (Amended) The method of claim 42, wherein the therapeutically effective dose is [about] 3,000 mg.

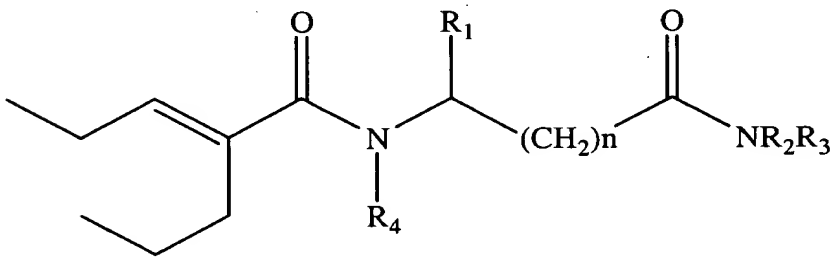
44. (Amended) The method of claim 42, wherein the therapeutically effective dose is [an amount from about 10 mg to about] 1,000 mg.

45. (Amended) The method of claim 44, wherein the therapeutically effective dose is [an amount from about 50 mg to about 500] 2,000 mg.

47. (Amended) A method of [preventing] pain prophylaxis in a subject predisposed to suffering from pain comprising periodically administering to the subject a prophylactically effective dose of a compound having the following structure:



or



wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the prophylactically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder; so as to thereby [prevent] effect pain prophylaxis in the subject.

55. (Amended) The method of claim [54] 47, wherein the [somatogenic] pain is neuropathic pain.

62. (Amended) The method of claim 47, wherein the prophylactically effective dose is an amount from [about 10] 1,000 mg to [about 6,000] 4,000 mg.

63. (Amended) The method of claim 62, wherein the prophylactically effective dose is an amount from [about 500] 1,000 mg to [about 4,000] 3,000 mg.

64. (Amended) The method of claim [62] 63, wherein the prophylactically effective dose is an amount from [about 10] 2,000 mg to [about] 3,000 mg.

65. (Amended) The method of claim 64, wherein the prophylactically effective dose is [about] 3,000 mg.

66. (Amended) The method of claim 64, wherein the prophylactically effective dose is [an amount from about 10 mg to about] 1,000 mg.

67. (Amended) The method of claim 66, wherein the prophylactically effective dose is [an amount from about 50 mg to about 500] 2,000 mg.

72. (Amended) The method of claim 68, wherein one or more of R_1, R_2, or R_3 [or R_4] is a linear chain C_1-C_6 alkyl group.

73. (Amended) The method of claim 68, wherein one or more of R_1, R_2, or R_3 [or R_4] is a branched chain C_1-C_6 alkyl group.

86. (Amended) The method of claim 68, wherein the prophylactically effective dose is an amount from [about 10] 1,000 mg to [about 6,000] 4,000 mg.

87. (Amended) The method of claim 86, wherein the prophylactically effective dose is an amount from [about 500] 1,000 mg to [about 4,000] 3,000 mg.

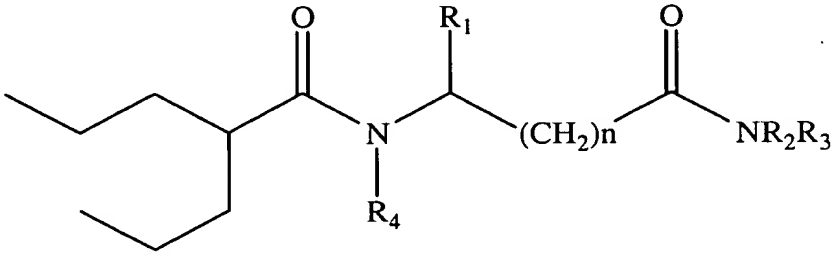
88. (Amended) The method of claim [86] 87, wherein the prophylactically effective dose is an amount from [about 10] 2,000 mg to [about] 3,000 mg.

89. (Amended) The method of claim 88, wherein the prophylactically effective dose is [about] 3,000 mg.

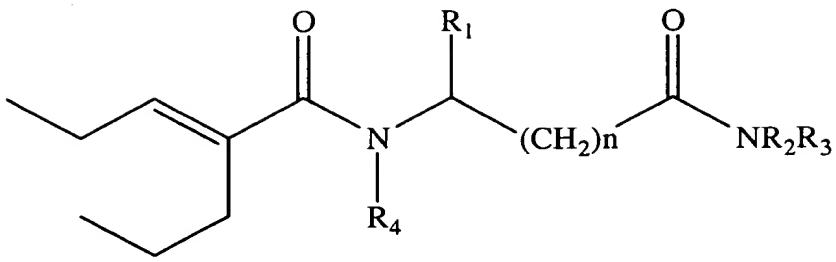
90. (Amended) The method of claim 88, wherein the prophylactically effective dose is [an amount from about 10 mg to about] 1,000 mg.

91. (Amended) The method of claim 90, wherein the prophylactically effective dose is [an amount from about 50 mg to about 500] 2,000 mg.

93. (Amended) A method of treating a subject suffering from pain comprising periodically administering to the subject a pharmaceutical composition comprising a therapeutically effective dose a compound having the following structure:

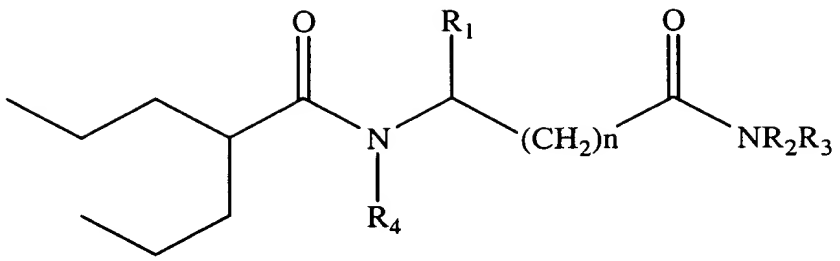


or

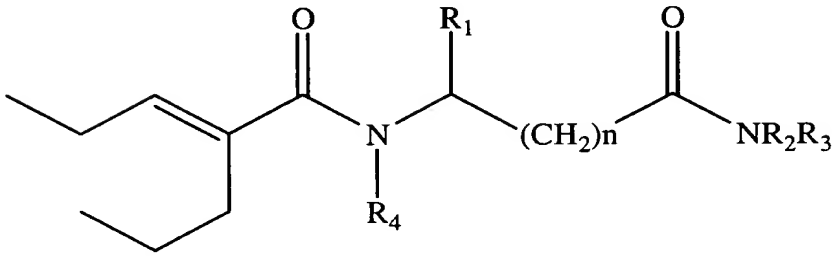


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, and a pharmaceutically acceptable carrier; wherein the therapeutically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder; so as to thereby treat the subject's pain.

94. (Amended) A method of [preventing] pain prophylaxis in a subject predisposed to suffering from pain comprising periodically administering to the subject a composition comprising a prophylactically effective dose of a compound having the following structure:

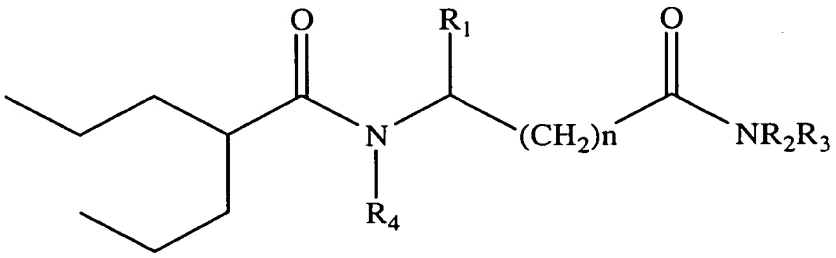


or

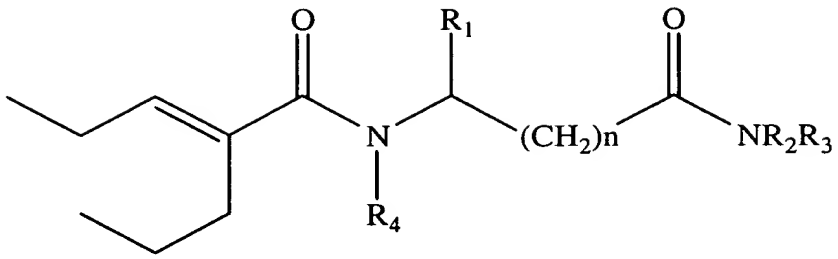


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, and a pharmaceutically acceptable carrier; wherein the therapeutically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder; so as to thereby [prevent] effect pain prophylaxis in the subject.

95. (Amended) A method of treating a subject suffering from a headache disorder comprising periodically administering to the subject a therapeutically effective dose of a compound having the following structure:

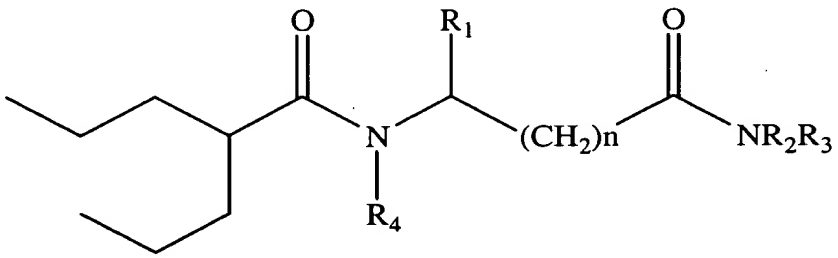


or

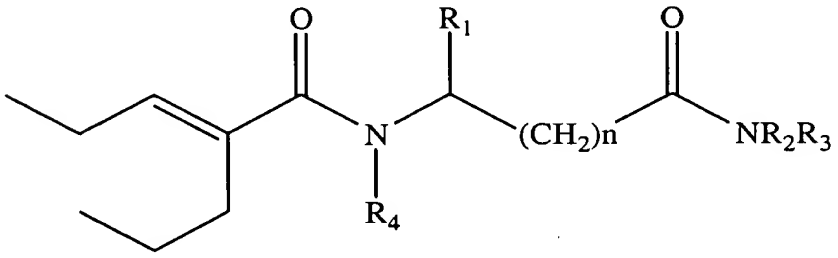


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the therapeutically effective dose is 1,000 to 6,000 mg; so as to thereby treat the headache disorder.

96. (Amended) A method of preventing a headache disorder in a subject predisposed to suffering from a headache disorder comprising periodically administering to the subject a prophylactically effective dose of a compound having the following structure:



or



wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the prophylatically effective dose is 1,000 to 6,000 mg; so as to thereby prevent the headache disorder in the subject.